TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		Attorney's Docket Number 70398
		U.S. Application No. (if known, see 37 C.F.R. 1.5) 10/018597
INTERNATIONAL APPLICATION NO. PCT/IT00/00227	INTERNATIONAL FILING DATE 5/June/2000	PRIORITY DATE CLAIMED 9/June/1999
TITLE OF INVENTION IONOPHORETIC DRUG DELIVERY DEVICE		
APPLICANT(S) FOR DO/EO/US D'AFRICA et al.		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.

2. [] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.

3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S.C. 371(C)(2))
   a. [ ] is transmitted herewith (required only If not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other documents (s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98

12. [] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.

14. [] A substitute specification.

15. [ ] A change of power of attorney and/or address letter.

16. [X] Other items or information:
    Formal Drawings (5 sheets)
    Copy of Express Mail Receipt No. EI 346 229 495 US
    Copies of Cited References (9)

U.S. Appln No. (if known, see 37 CFR 15) 10701859	International Application No. PCT/IT00/00227	Attorney's Docket Number 70398

17. [X] The following fees are submitted: **BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):**	CALCULATIONS PTO USE ONLY
Search Report has been prepared by the EPO or JPO $890.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) $710.00	
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $740.00	
Neither international preliminary examination fee (37 CFR 1.482 nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,040.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of $130 00 for furnishing the oath or declaration later than [ ]20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e))	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	18 - 20 =	0	X $ 18.00	$	
Independent claims	2 - 3 =	0	X $ 84.00	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $280.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 890.00	

Reduction of 1/2 for filing small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1,28)	$	
SUBTOTAL =	$ 890.00	
Processing fee of $130.00 for furnishing the English translation late than [ ]20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +	$	
TOTAL NATIONAL FEE =	$ 890.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +	$	
TOTAL FEES ENCLOSED =	$ 890.00	
	Amount to be: refunded	$
	charged	$

a. [X] A check in the amount of $ 890.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. 13-0410 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13.0410. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:

McGLEW AND TUTTLE, P.C.
Scarborough Station
Scarborough, NY 10510-0827

Signature

John James McGlew
Name

31,903
Registration Number

ATTORNEY DOCKET NO: 70398

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	D'AFRICA et al.
Serial No	:	
Confirm. No	:	
Filed	:	
For	:	IONOPHORETIC DRUG DELIVERY DEVICE
Art Unit	:	
Examiner	:	
Dated	:	December 7, 2001

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend claims 1 through 18 as follows on the next two pages. A marked up version showing changes to the claims is attached at the end of this amendment.

AMENDED CLAIMS

1. Device for the transdermal administration of an active compound, comprising a current generator and at least one pair of electrodes for application to a patient, one of which must be suitable for holding a vehicle containing the active compound, characterized in that said generator generates a one-way current between said electrodes which is modulated in amplitude by a modulator of a periodic nature.

2. Device according to Claim 1, characterized in that said modulator has an amplitude which can vary between zero and a maximum value.

3. Device according to Claim 1, characterized in that the one-way current has a positive sinusoidal waveform.

4. Device according to Claim 1, characterized in that the one-way current has a rectified sinusoidal waveform.

5. Device according to Claim 1, characterized in that the one-way current has a half-sinusoidal waveform.

6. Device according to Claim 1, characterized in that the one-way current has a triangular or sawtooth waveform.

7. Device according to Claim 1, characterized in that the one-way current has a square waveform.

8. Device according to Claim 1, characterized in that the modulator has a waveform selected from the group comprising: a triangular waveform, a rectified sinusoidal waveform, a half-sinusoidal waveform or combinations thereof.

9. Device according to Claim 1, characterized in that the one-way current has a frequency of between 100 and 3000 Hz.

10. Device according to Claim 1, characterized in that the modulator has a frequency between 0.1 and 5 Hz and preferably between 0.5 and 1 Hz.

11. Device according to Claim 1, characterized in that the current applied between the electrodes has a

maximum value of 100 mA.

12. Method of administering an active compound by transdermal means, comprising the stages of:

- applying two electrodes, one of which is associated with a vehicle containing the active compound,
- generating a one-way current between the two said electrodes which is modulated in amplitude by a modulating signal of a periodic nature.

13. Method according to Claim 12, characterized in that said one-way current has a waveform selected from the group comprising: a rectified sinusoidal wave, a half-sinusoidal wave, a sawtooth wave, a triangular wave, a square wave, a positive sinusoidal wave, a train of pulses.

14. Method according to Claim 12, characterized in that said modulator has a waveform selected from the group comprising: a triangular waveform, a sawtooth waveform, a rectified sinusoidal waveform, a half-sinusoidal waveform or combinations thereof.

15. Method according to Claim 12, characterized in that said modulating signal has an amplitude which can be varied between zero and a maximum value.

16. Method according to Claim 12, characterized in that said one-way current has a frequency of between 100 and 3000 Hz.

17. Method according to Claim 12, characterized in that said modulating signal has a frequency of between 0.1 and 5 Hz and preferably between 0.5 and 1 Hz.

18. Method according to Claim 12, characterized in that the current between said electrodes varies between zero and a maximum value equal to 100 mA.

REMARKS

All changes to claims 1 through 18 are to remove the multiple dependency of the original claims. No new matter has been added.

Favorable action on the merits of this application is respectfully requested.

Respectfully submitted
for Applicant,

By: ____________________
John James McGlew
Registration No. 31,903
McGLEW AND TUTTLE, P.C.

Attached: Marked-up Version of Claims Showing Changes

JJM:esd
70398.1

DATED: December 7, 2001
SCARBOROUGH STATION
SCARBOROUGH, NEW YORK 10510-0827
(914) 941-5600

SHOULD ANY OTHER FEE BE REQUIRED, THE PATENT AND TRADEMARK OFFICE IS HEREBY REQUESTED TO CHARGE SUCH FEE TO OUR DEPOSIT ACCOUNT 13-0410.

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231, NO.: EL 346 229 495 US

McGLEW AND TUTTLE, P.C.
SCARBOROUGH STATION, SCARBOROUGH, NY 10510-0827

BY: ____________________ DATE: December 7, 2001

MARKED-UP CLAIMS

1. Device for the transdermal administration of an active compound, comprising a current generator and at least one pair of electrodes for application to a patient, one of which must be suitable for holding a vehicle containing the active compound, characterized in that said generator generates a one-way current between said electrodes which is modulated in amplitude by a modulator of a periodic nature.

2. Device according to Claim 1, characterized in that said modulator has an amplitude which can vary between zero and a maximum value.

3. Device according to Claim 1 [or 2] characterized in that the one-way current has a positive sinusoidal waveform.

4. Device according to Claim 1 [or 2] characterized in that the one-way current has a rectified sinusoidal waveform.

5. Device according to Claim 1 [or 2] characterized in that the one-way current has a half-sinusoidal waveform.

6. Device according to Claim 1 [or 2] characterized in that the one-way current has a triangular or sawtooth waveform.

7. Device according to Claim 1 [or 2] characterized in that the one-way current has a square waveform.

8. Device according to [one or more of the foregoing] Claim[s] 1, characterized in that the modulator has a waveform selected from the group comprising: a triangular waveform, a rectified sinusoidal waveform, a half-sinusoidal waveform or combinations thereof.

9. Device according to [one or more of the foregoing] Claim[s] 1, characterized in that the one-way current has a frequency of between 100 and 3000 Hz.

10. Device according to [one or more of the foregoing] Claim[s] 1, characterized in that the modulator has a frequency between 0.1 and 5 Hz and preferably between 0.5 and 1 Hz.

11. Device according to [one or more of the foregoing] Claim[s] 1, characterized in that the current applied between the electrodes has a

maximum value of 100 mA.

12. Method of administering an active compound by transdermal means, comprising the stages of:

- applying two electrodes, one of which is associated with a vehicle containing the active compound,
- generating a one-way current between the two said electrodes which is modulated in amplitude by a modulating signal of a periodic nature.

13. Method according to Claim 12, characterized in that said one-way current has a waveform selected from the group comprising: a rectified sinusoidal wave, a half-sinusoidal wave, a sawtooth wave, a triangular wave, a square wave, a positive sinusoidal wave, a train of pulses.

14. Method according to Claim[s] 12 [or 13], characterized in that said modulator has a waveform selected from the group comprising: a triangular waveform, a sawtooth waveform, a rectified sinusoidal waveform, a half-sinusoidal waveform or combinations thereof.

15. Method according to Claim[s] 12, [13 or 14,] characterized in that said modulating signal has an amplitude which can be varied between zero and a maximum value.

16. Method according to [one or more of] Claim[s] 12 [to 15], characterized in that said one-way current has a frequency of between 100 and 3000 Hz.

17. Method according to [one or more of] Claim[s] 12 [to 16], characterized in that said modulating signal has a frequency of between 0.1 and 5 Hz and preferably between 0.5 and 1 Hz.

18. Method according to [one or more of the foregoing] Claim[s,] 12, characterized in that the current between said electrodes varies between zero and a maximum value equal to 100 mA.

IONOPHORETIC DRUG DELIVERY DEVICE

DESCRIPTION

This invention relates to a device and method for the transdermal administration of active compounds by hydroelectrophoresis and ionophoresis.

It is known that active compounds of various kinds can be administered by ionophoresis, by applying two electrodes to the patient, one of which is fitted with means for holding a solution containing the active compound being administered, while the other electrode comprises a metal plate. The two electrodes are connected electrically to a current generator, normally of the single direction pulsed type. Ions are generated and pass through the barrier represented by the epidermis and enter the underlying tissues, where they are absorbed by the body.

Active compounds of various kinds having a therapeutic effect and even a cosmetic effect are administered using this technique. For example, in the more strictly therapeutic sector, ionophoresis is used for the administration of calcium chloride and magnesium chloride solutions as an analgesic, hydrocortisones and other anti-inflammatories and other products.

Devices and electrodes of a special shape for the transdermal administration of active compounds are described in EP-A-0292930, US-A-5,084,008, WO-A-8808729, WO-A-9622810.

The currents used in these administration techniques may be of various forms. In general one-way pulsed or sinusoidal currents which may be frequency-modulated, amplitude-modulated and in some cases both frequency-modulated and amplitude-modulated are used.

The ionophoretic method has some defects however, the main one being the poor efficiency of transdermal transport and distribution of the active compound almost exclusively in the surface areas of tissue.

A technical improvement in ionophoresis has recently been suggested which uses a frozen solution of active compound (cryoelectrophoresis) which however has the disadvantage of appreciable surface dispersion of the drug during treatment as a result of the Joule effect, with the result that a maximum

of only 5% of the active compound can be transported. It is also true that cryoelectrophoresis does not introduce the drug into the systemic circulation, but this is exclusively due to vasoconstriction at the points of contact between the frozen solution and the skin, and the fact that in the physical condition of the solution (solid) electrophoretic mobility is zero.

Surprisingly it has now been found, and this constitutes the subject matter of this invention, that a particular conformation of the current waveform and the voltage between the electrodes favours the administration of active compounds via the transdermal route in comparison with the waveforms conventionally used.

In substance, in accordance with the invention a device is provided for the transdermal administration of an active compound comprising electrodes which are to be applied to a patient, one of which is capable of holding a vehicle containing the active compound, characterized in that the generator generates a one-way amplitude-modulated current between said electrodes by means of a modulator having a periodical function.

By one-way current is generically meant any current having a constant sign, and therefore capable of generating an ionophoretic effect, which varies periodically between a minimum value and a maximum value. The maximum value, and therefore the maximum amplitude of the current voltage between the electrodes, is modulated by means of a periodical modulating signal, e.g. a triangular waveform.

The modulating signal may have a variable course between a minimum value and a maximum value, where the minimum value is preferably equal to zero.

The one-way current may have a waveform selected from the group comprising: a positive sinusoidal waveform, a rectified sinusoidal waveform, a half-sinusoidal waveform, a triangular or sawtooth waveform, a square waveform or equivalent waveforms periodically oscillating between zero and a maximum amplitude value modulated as above.

The modulating signal may have a waveform selected from the group comprising: a triangular waveform, a rectified sinusoidal waveform, a half-

sinusoidal waveform, a trapezoidal waveform, or combinations thereof.

The invention also relates to a method for the administration of an active compound via the transdermal route comprising the stages of:

- applying two electrodes, one of which is associated with a vehicle containing the active compound,
- generating a one-way current which is amplitude-modulated by a modulating signal of a periodical nature between said two electrodes.

Further advantageous features of the device and the method according to the invention are indicated in the dependent claims and in the following description of some embodiments.

The invention will be better understood from the description and the appended drawing, which illustrates non-restrictive embodiments of the invention. The various figures and in particular the waveform diagrams are indicative and not to scale. In the drawing:

Figure 1 shows a diagram of the equipment for transdermal molecular transport,

Figure 2 shows the waveform of the carrier signal,

Figure 3 shows the waveform of the modulating signal,

Figure 4 shows the modulated waveform for the current generated by the device,

Figures 5 to 9 show other possible waveforms for the carrier signal,

Figures 10 to 12 show other alternative forms of the modulating signal,

Figure 13 shows a modulated waveform with a triangular modulator, and

Figure 14 shows diagrams of experimental data.

Figure 1 shows, extremely diagrammatically, equipment for transdermal molecular transport generically indicated by 1 to which are attached two electrodes 3 and 5, connected to equipment 1 by means of wires 7 and 9. Electrode 5 is generically a flexible metal sheet which can be applied so that it fits the anatomical shape of the area of the patient's body to which the electrode has to be applied, and this will normally be a negative electrode. Electrode 3, generally positive, is constructed in such a way as to contain an

active compound which has to be administered by transdermal means. The active compound is normally held in a liquid or frozen solution, in a gel or in other means. For the purposes of this invention the method by which the active compound is held on electrode 3 and released by it is not restrictive, and likewise the nature of the active compound, which may be a drug, for example an analgesic or anaesthetic, a product for the treatment of skin blemishes, cellulitis or the like, is not restrictive. However, optimum results are obtained with active compounds suspended in gels, e.g. agarose.

The conformation of the electrodes and the generator are known to those skilled in the art and will not be described in greater detail here.

In accordance with the invention the current generated between electrodes 3 and 5 has a special waveform comprising an amplitude-modulated signal obtained from the modulation of a carrier signal comprising e.g. a rectified sinusoidal wave or the like.

Figure 2 represents by way of example a first waveform for which the carrier signal comprises a rectified sinusoidal wave. This signal has a frequency typically between 100 and 3000 Hz. A greater depth of penetration by the ions or molecules of the active compound conveyed through the electric field generated between two electrodes 3 and 5 is obtained at lower frequencies. The carrier signal illustrated in Figure 2 is modulated e.g. by means of a sawtooth modulating signal of the type shown in Figure 3. The frequency of the modulating signal may lie e.g. between 0.1 and 5 Hz and preferably between 0.5 and 1 Hz.

Figure 4 shows the current waveform and the voltage between the electrodes applied to the patient obtained with the modulator in Figure 3 applied to the carrier in Figure 2. Typically the currents used have a maximum strength of approximately 100 mA.

The application of an oscillating voltage having an amplitude which is modulated in a periodic way as illustrated in Figure 4 results in improved transdermal transfer capacity for the active compounds. Similar results can be obtained by using various waveforms for the carrier signal and various waveforms for the modulating signal, provided that the basic principle

represented by the fact that the carrier signal is amplitude-modulated by a modulating signal of a periodic form which varies between zero and a maximum value is maintained.

Figures 5 to 9 show examples of carrier signals constituted in the order of: a positive sinusoidal waveform, a triangular waveform, a positive square waveform, a sawtooth waveform, a series of spaced pulses.

These carrier signals can be modulated with a modulator having the sawtooth waveform in Figure 3, and also by different modulators, e.g. of triangular shape as in Figure 10 or rectified sinusoidal as in Figure 11 or trapezoidal as in Figure 12.

Figure 13 shows the waveform which can be obtained from modulating the signal in Figure 2 by the modulator in Figure 10.

In this figure, as in the preceding figures, the waveforms are merely indicative, in particular the ratios between the frequency of the base signal and the modulator are not respected.

The efficiency of the waveform according to the invention in comparison with conventional cryoelectrophoresis techniques was tested using the following method.

Progesterone solutions labelled with 1.125 cpm (Byk) 3800 cpm were used. Radioactivity was measured using the SR 300 Tratec (Byk) automatic instrument.

Treatment was applied to adult rabbits of the New Zealand variety having a mean weight of 1.980 kg which had been shaved in the pubic and thoracic areas.

Urine samples were obtained using an echography syringe. Blood samples were obtained from the auricular vein.

18 rabbits subdivided into four groups were used, and of these the first three, each consisting of 4 rabbits, were treated by hydroelectrophoresis using labelled progesterone, the third group comprising 3 subgroups of 2 rabbits by cryoelectrophoresis using labelled progesterone.

Determinations level with the skin, 3 cm from the skin and 6 cm from the skin were performed in all the groups. The tissues were homogenized and

dissolved in 2.5 ml of 1 N NaOH and the radioactivity of the solutions was measured. Administration was performed using currents at 500, 1000 and 2000 Hz.

The results are shown in Figure 13.

After treatment by cryoelectrophoresis in the pubic area at 1000 Hz the radioactivity found in urine was 5% of the total, while with hydroelectrophoresis the measured radioactivity was 79.6%. Activity measured in the lungs 6 cm from the skin and at a frequency of 500 Hz was 74.7% for ionophoresis and only 2% for cryoelectrophoresis.

CONCLUSIONS

The radioactivity measurements indicate that cryoelectrophoresis is wholly ineffective for transdermal transport of the labelled compound used.

This result is explained by the zero electrophoretic mobility of substances in the solid state and the small amount of radioactivity measured in the tissues is due to melting of the solid in contact with the skin and subsequent passage due to ionophoresis.

Hydroelectrophoresis using an agarose gel improved migration of the radioactive compound while the electrical field was active, and the use of the waveform according to the invention created an ideal ionic force for favouring the transdermal passage of labelled progesterone.

It can be concluded that hydroelectrophoresis performed using the waveform according to this invention is an effectively innovative procedure in the transdermal transport of drugs, whether or not they can be ionized.

In the case of non-ionizable molecules penetration is obtained as a result of the polarizability of the molecules. The polarized molecules migrate through the skin, and in particular through the pores, under the effect of the applied electric field.

It is to be understood that the drawing only shows one embodiment merely provided as a practical demonstration of the invention, and said invention may vary in form and arrangement without however going beyond the scope of the concept underlying the invention itself. Any reference numbers present in the attached claims are designed to assist reading of the

claims with reference to the description and the drawing, and do not restrict the scope of the protection covered by the claims.

CLAIMS

1. Device for the transdermal administration of an active compound, comprising a current generator and at least one pair of electrodes for application to a patient, one of which must be suitable for holding a vehicle containing the active compound, characterized in that said generator generates a one-way current between said electrodes which is modulated in amplitude by a modulator of a periodic nature.

2. Device according to Claim 1, characterized in that said modulator has an amplitude which can vary between zero and a maximum value.

3. Device according to Claim 1 or 2, characterized in that the one-way current has a positive sinusoidal waveform.

4. Device according to Claim 1 or 2, characterized in that the one-way current has a rectified sinusoidal waveform.

5. Device according to Claim 1 or 2, characterized in that the one-way current has a half-sinusoidal waveform.

6. Device according to Claim 1 or 2, characterized in that the one-way current has a triangular or sawtooth waveform.

7. Device according to Claim 1 or 2, characterized in that the one-way current has a square waveform.

8. Device according to one or more of the foregoing Claims, characterized in that the modulator has a waveform selected from the group comprising: a triangular waveform, a rectified sinusoidal waveform, a half-sinusoidal waveform or combinations thereof.

9. Device according to one or more of the foregoing Claims, characterized in that the one-way current has a frequency of between 100 and 3000 Hz.

10. Device according to one or more of the foregoing Claims, characterized in that the modulator has a frequency between 0.1 and 5 Hz and preferably between 0.5 and 1 Hz.

11. Device according to one or more of the foregoing Claims, characterized in that the current applied between the electrodes has a

maximum value of 100 mA.

12. Method of administering an active compound by transdermal means, comprising the stages of:

- applying two electrodes, one of which is associated with a vehicle containing the active compound,
- generating a one-way current between the two said electrodes which is modulated in amplitude by a modulating signal of a periodic nature.

13. Method according to Claim 12, characterized in that said one-way current has a waveform selected from the group comprising: a rectified sinusoidal wave, a half-sinusoidal wave, a sawtooth wave, a triangular wave, a square wave, a positive sinusoidal wave, a train of pulses.

14. Method according to Claims 12 or 13, characterized in that said modulator has a waveform selected from the group comprising: a triangular waveform, a sawtooth waveform, a rectified sinusoidal waveform, a half-sinusoidal waveform or combinations thereof.

15. Method according to Claims 12, 13 or 14, characterized in that said modulating signal has an amplitude which can be varied between zero and a maximum value.

16. Method according to one or more of Claims 12 to 15, characterized in that said one-way current has a frequency of between 100 and 3000 Hz.

17. Method according to one or more of Claims 12 to 16, characterized in that said modulating signal has a frequency of between 0.1 and 5 Hz and preferably between 0.5 and 1 Hz.

18. Method according to one or more of the foregoing Claims, characterized in that the current between said electrodes varies between zero and a maximum value equal to 100 mA.

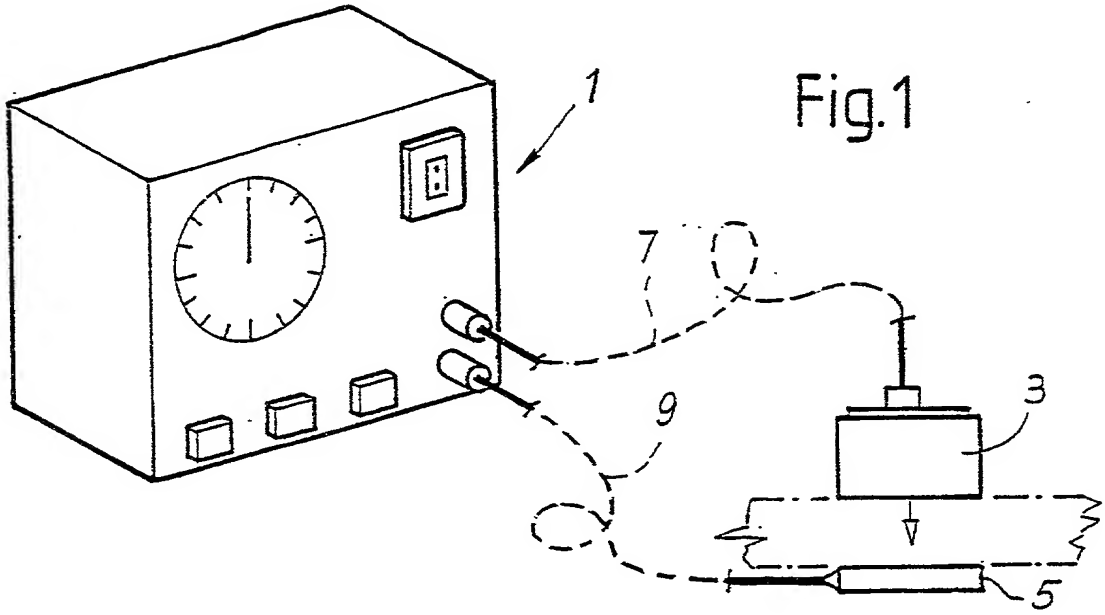


Fig.1

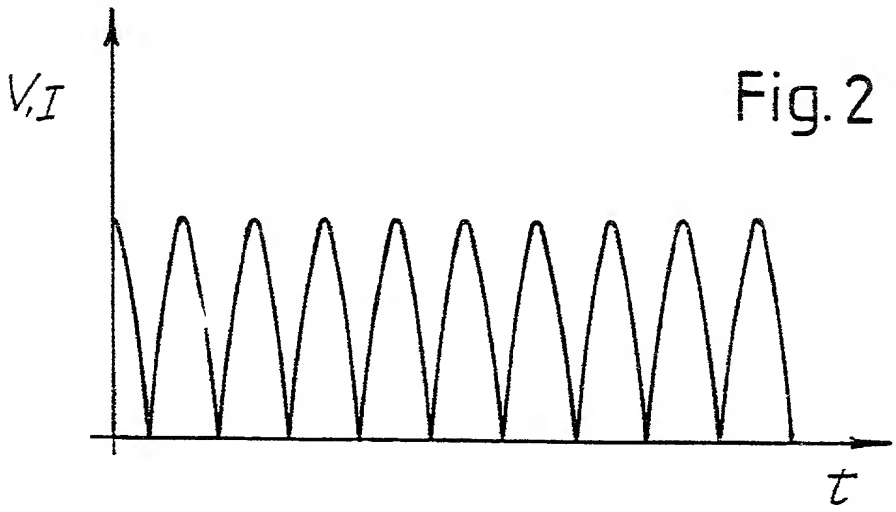


Fig. 2

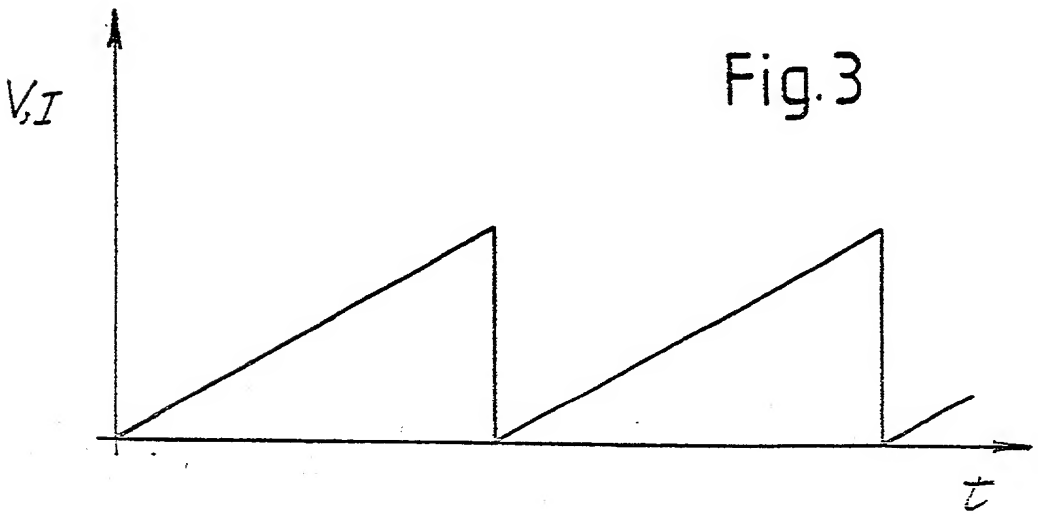


Fig. 3

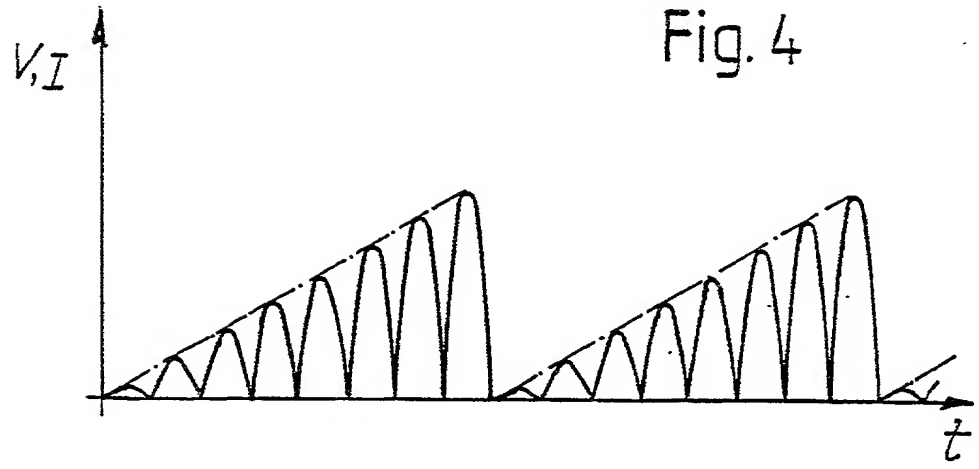


Fig. 4

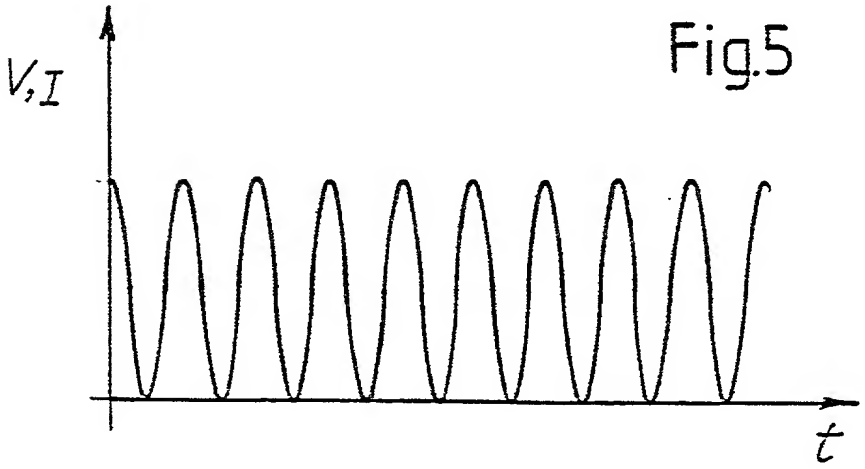


Fig.5

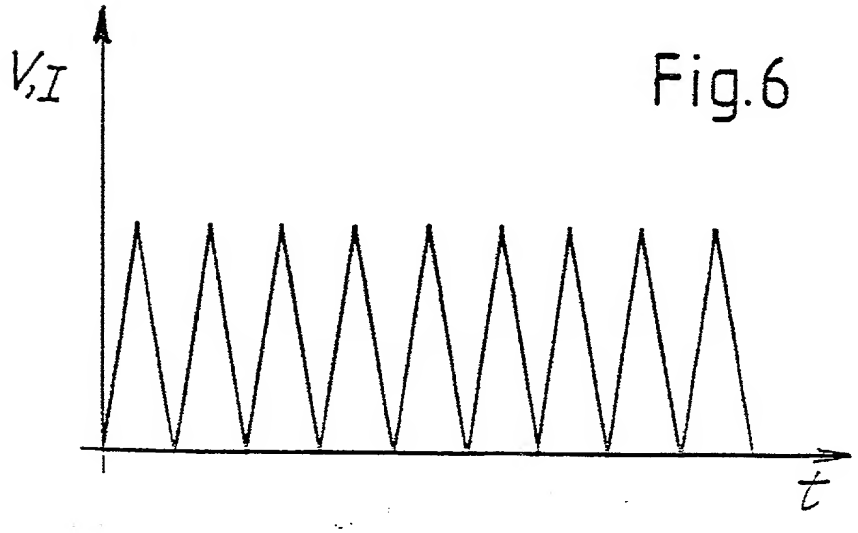


Fig.6

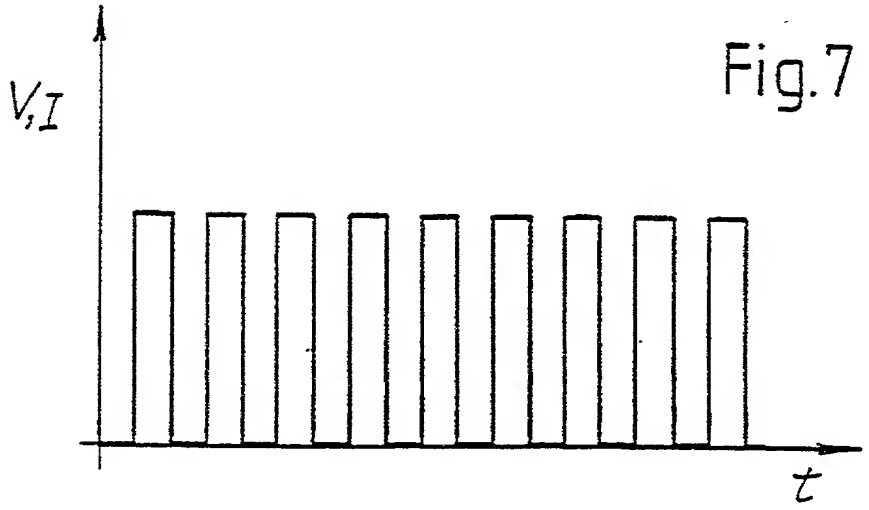


Fig.7

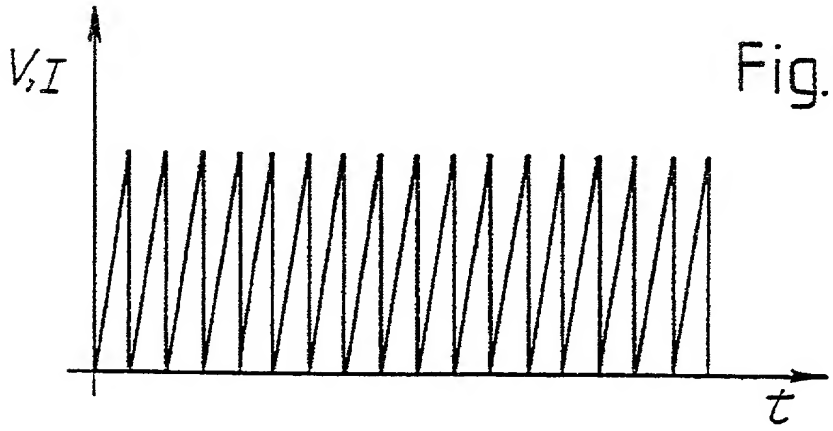


Fig.8

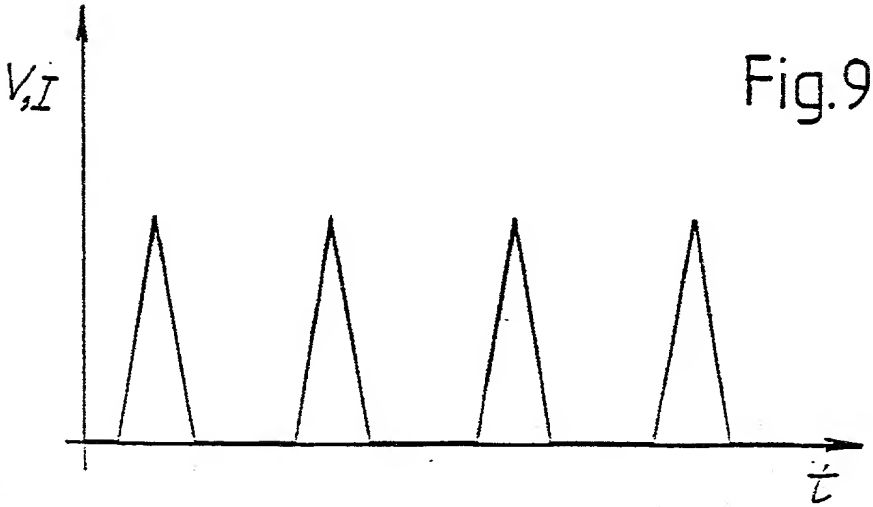


Fig.9

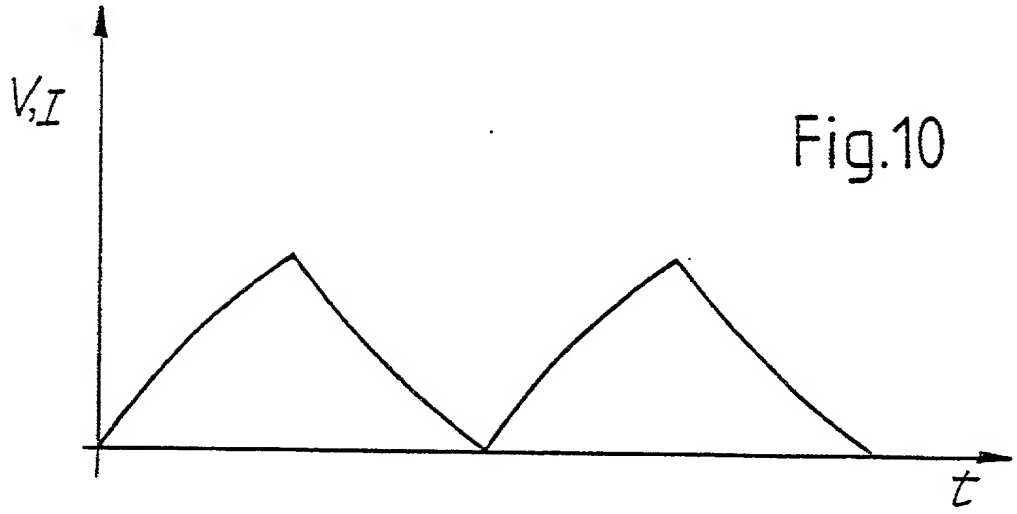


Fig.10

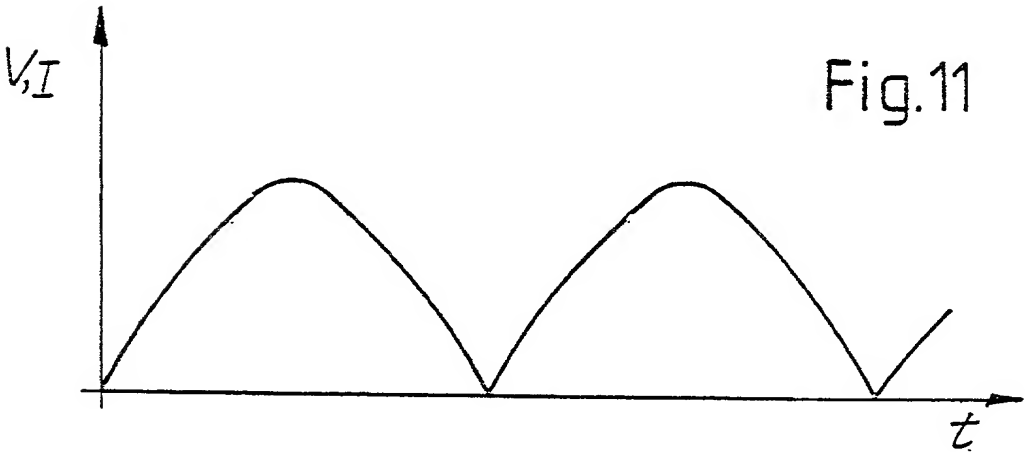
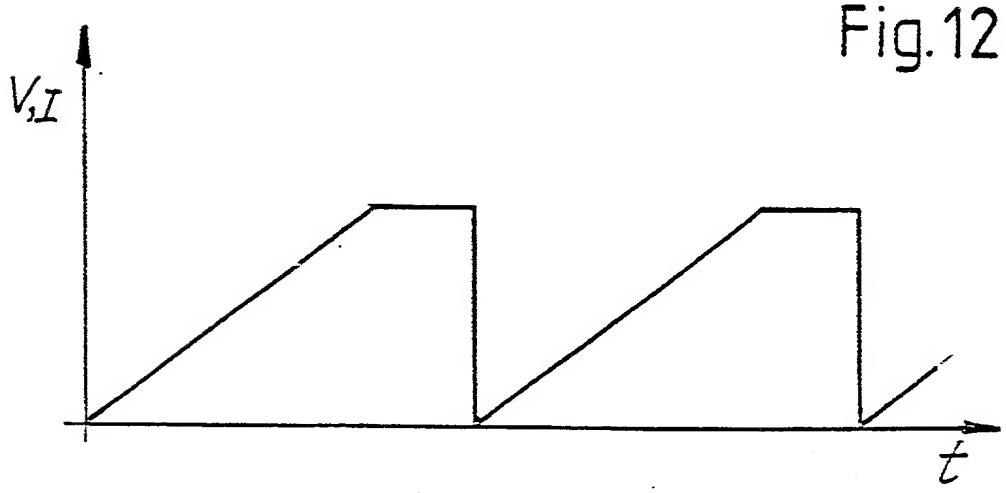


Fig.11

Fig.12



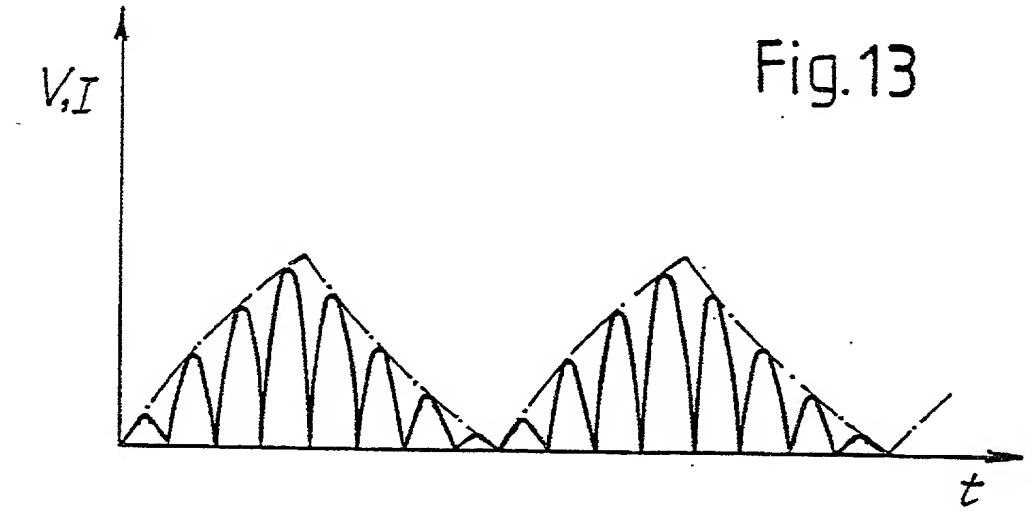


Fig.13

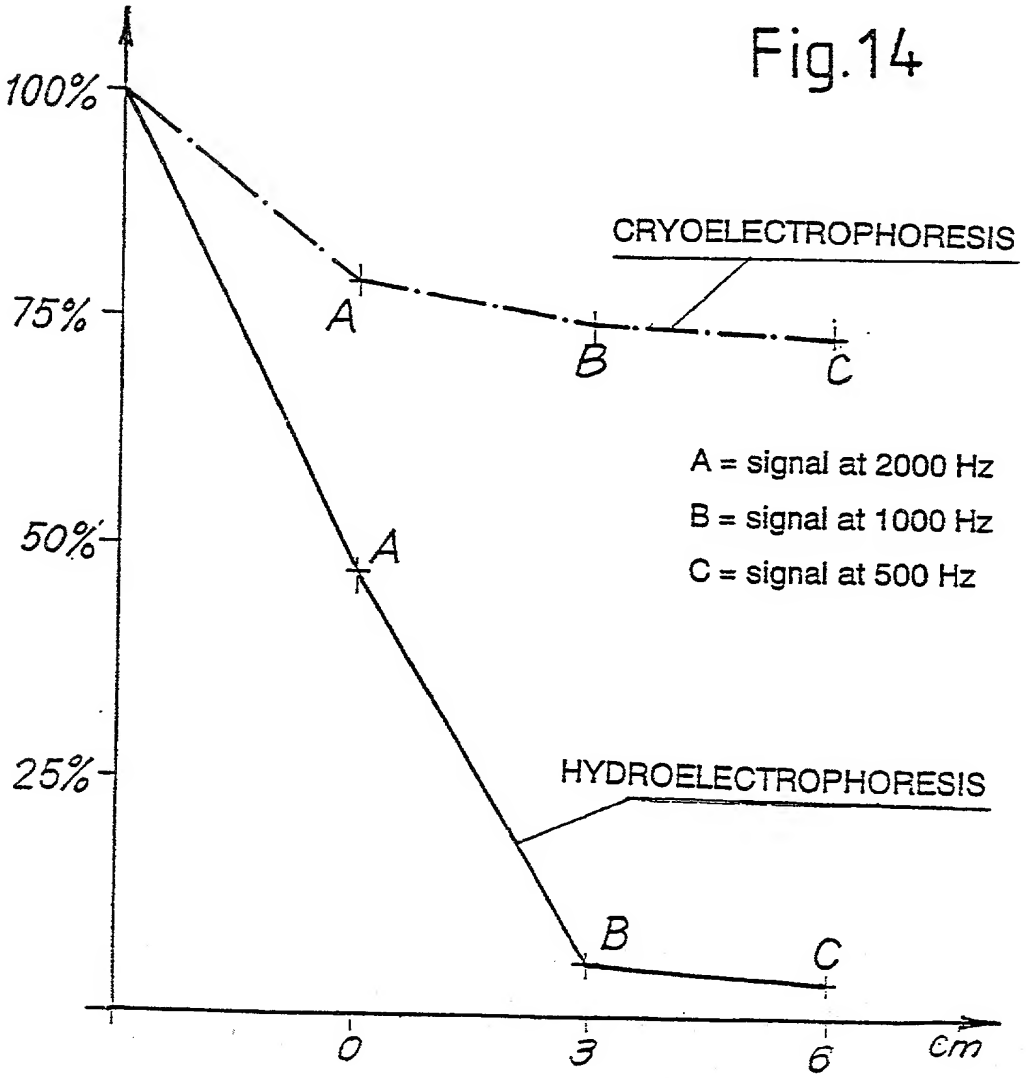


Fig.14

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION **ATTY. DOCKET NO._____**

As a below named inventor, I hereby declare that:
My residence/post office address and citizenship are as stated below next to my name;
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IONOPHORETIC DRUG DELIVERY DEVICE

the specification of which is attached hereto unless the following box is checked:

( ) was filed in the U.S. on __
as U.S. Application Serial No._____ ; or

(X) PCT International Application Number PCT/ITOO/00227 and was amended on June 5, 2000 (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority
I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY:	APPLICATION No.:	DATE FILED: Day/Month/Year	PRIORITY CLAIMED UNDER 35 U.S.C. 119
ITALY	FI99A000141	09.06.1999	YES: X ~~NO~~:____
			YES:____ NO:____

U.S. Priority Claim
I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL No.:	FILING DATE: Day/Month/Year	STATUS (patented/pending/abandoned)

POWER OF ATTORNEY:

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) listed below to prosecute this application and transact all business in the Patent and Trademark Office connected therewith; we further hereby authorize the following attorney(s) and/or agent(s) to insert the correct serial number and filing date into this declaration, if none is indicated on that date of our execution of this Declaration.

John J. McGlew, Reg. 17,722; and/or John James McGlew, Reg. 31,903; and/or Hilda S. McGlew, Reg. 30,295; and/or Theobald Dengler, Reg. 34,575; and/or Keith D. Moore, Reg. 44,951.

Send Correspondence to:	**Direct Telephone Calls To:**
McGLEW AND TUTTLE, P.C.	John James McGlew
SCARBOROUGH STATION	(914) 941-5600
SCARBOROUGH, NEW YORK 10510-0827	
Customer No.: 23872	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

& Full Name of sole or first Inventor: D'AFRICA Antonino

Citizenship: Italy

Residence: Via Modena S. Sperato II trav. 46, 89100 REGGIO CALABRIA Italy

I-IX

Post Office Address: Via Modena S. Sperato II trav. 46, 89100 REGGIO CALABRIA Italy

Inventor's Signature: X _____ Date: 27.11.2001

Day/Month/Year

& Full Name of second Inventor: PADUANO Guido

& Citizenship: Italy

Residence: Via Roma 12, 22067 MISSAGLIA, LECCO Italy

Post Office Address Via Roma 12, 22067 MISSAGLIA, LECCO Italy

Inventor's Signature: X ______________________ Date: 27.11.2001
Day/Month/Year

& Full Name of third Inventor: SARTORI Massimo

Citizenship: Italy

Residence: Via del Faggio, 22, 22060 CARIMATE, COMO Italy

Post Office Address: Via del Faggio, 22, 22060 CARIMATE, COMO Italy

Inventor's Signature: X ______________________ Date: 27.11.2001
Day/Month/Year

& Full Name of fourth Inventor: ______________________

Citizenship: ______________________

Residence: ______________________

Post Office Address: ______________________

Inventor's Signature: ______________________ Date: __________
Day/Month/Year

& Full Name of fifth Inventor: ______________________

Citizenship: ______________________

Residence: ______________________

Post Office Address: ______________________

Inventor's Signature: ______________________ Date: __________
Day/Month/Year